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PRINCIPAL INVESTIGATOR: George Verghese

CONTRACTING ORGANIZATION : Massachusetts Institute of Technology
Cambridge, MA 02139

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George Verghese, Professor of Electrical and Biomedical Engineering

E-Mail: verghese@mit.edu

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77 Massachusetts Avenue
Cambridge MA 02139

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14. ABSTRACT The project aims (i) to further develop and validate a novel model-based approach to noninvasive, calibration-free determination of intracranial pressure (ICP) from quantities that are routinely measured in clinical settings, and (ii) to initiate the creation of a publicly available reference database of physiological signals collected from brain injury patients. Our noninvasive ICP (nICP) estimate requires simultaneous measurement of the waveforms of arterial blood pressure (ABP), obtained via radial artery catheter or finger cuff, and of cerebral blood flow velocity (CBFV) at a major cerebral artery, measured by transcranial Doppler (TCD). The target population for our initial database comprises subarachnoid hemorrhage patients in neuro-intensive care at our partner hospital, for whom ICP, ABP and CBFV are currently measured as the clinical standard of care. Our major accomplishments so far on this project include: assembling a component-based system to support data collection and processing in the intensive care setting; converting our earlier batch-mode nICP estimation algorithms to run continuously and in real time; developing the associated software and user interfaces; arranging for the data-collection modalities to satisfy an existing IRB that allows the collected data to be transferred to the publicly accessible MIMIC II database; and familiarizing the hospital staff with the equipment and procedures. We have also continued to work on developing signal-quality metrics, and have refinements and extensions of the underlying estimation algorithms.

15. SUBJECT TERMS
Intracranial pressure, noninvasive monitoring, cerebrovascular model, cerebral blood flow velocity, transcranial Doppler (TCD), traumatic brain injury (TBI)

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Table of Contents

I. Introduction

Intracranial pressure (ICP) is the pressure of cerebrospinal fluid (CSF) in the cranial cavity, and is an important "cranial vital sign" to monitor in patients with, or suspected of having sustained, an injury to the brain. However, current ICP measurement modalities are quite invasive, requiring penetration of the skull and the placing a sensor in the brain parenchyma or advancing a catheter to the intraventricular space. ICP measurement is therefore usually reserved for cases of severe injury only, and for situations where the required neurosurgical expertise is available, thus excluding a large proportion of patients whose diagnosis and treatment could benefit from ICP measurements. Furthermore, no front-line device currently exists for medics to assess, track, and manage ICP in theater or during transport to a fully equipped trauma-care center. An accurate method for noninvasive and continuous tracking of ICP will have tremendous and immediate value for early diagnosis and treatment of brain injury, titration of therapy, and monitoring of disease progression. There is accordingly a need for a thoroughly validated, noninvasive method to assess and track ICP (and therefore cerebral perfusion pressure), ideally continuously, robustly, in a patient-specific manner, and without the need for calibration. This project aims at further development of the algorithms, associated hardware, and clinical data collection required for validation of a novel approach to noninvasive ICP estimation that holds promise of meeting these criteria.

II. Objectives

The project aims are (i) to further develop and validate a novel model-based approach to noninvasive, calibration-free determination of ICP from quantities that are routinely measured in clinical settings, and (ii) to initiate the creation of a publicly available reference database of physiological signals collected from brain injury patients. Our noninvasive ICP (nICP) estimate requires simultaneous measurement of the waveforms of arterial blood pressure (ABP), obtained via radial artery catheter or finger cuff, and of cerebral blood flow velocity (CBFV) at a major cerebral artery, measured by transcranial Doppler (TCD). Our data collection is accordingly focused on recording ABP, CBFV and invasive ICP (for validation purposes), though other routinely monitored data and patient data is also collected.

More specifically, we aim to accomplish the following by the end of the project:

1. **Develop a high-resolution data-acquisition infrastructure** at the Neurological Intensive Care Unit (neuro-ICU) at Boston's Beth Israel Deaconess Medical Center (BIDMC), for time-locked collection of standard bedside monitoring data along with continuous cerebral blood flow velocity signals and invasively measured intracranial pressure (ICP) recordings.

2. **Establish a framework for archiving continuous monitoring data** and relevant clinical information from patients with critical brain injuries, to facilitate collection during and beyond this one-year project, and to allow the resulting de-identified database to be made available on an on-going basis to the interested research community.

3. **Seed the database** with monitoring data and clinical information collected over the entire multi-day neuro-ICU stay of 30 patients with critical brain injuries expected to be admitted to the BIDMC during the project year, and make the resulting initial de-identified database available to the interested research community.

4. **Validate our noninvasive ICP estimates** against this initial database of brain-injury patients, and determine whether our incorporation of high-resolution measurements further reduces the bias and improves the precision from those demonstrated in our prior work, yielding ICP estimates that lie within clinically acceptable tolerances.

5. **Demonstrate real-time performance** of the validated noninvasive ICP estimation algorithm.

III. Noninvasive ICP Estimation

To provide some context for reporting progress on the project, we briefly outline the basis of our approach to noninvasive ICP (nICP) estimation. Additional details may be found in [1], which describes the method more fully, along with the results of our initial validation experiments – carried out prior to the current project – using archived data from a collaborator.

The method uses a highly simplified dynamic model of the cerebral vasculature to relate the following three variables on an intra-heartbeat time scale: ICP, ABP, and cerebral blood flow (CBF) in a major cerebral artery, typically the middle cerebral artery (MCA). Although one would ideally like the ABP at the MCA, this is impractical, so we measure the ABP at the wrist or finger, and apply a carefully picked (and model-based) time-offset correction to adjust for the different relative distances from heart-to-wrist (or finger) versus heart-to-MCA. Two parameters enter the model: an aggregate cerebrovascular compliance *C,* representing the combined compliance of the arteries and brain tissue as seen from the MCA, and an aggregate cerebrovascular resistance *R*, representing the resistance of the blood flow path downstream from the MCA. A final assumption underlying the method is that CBF and CBFV are related by a simple scale factor on any estimation window.

With this set-up, measurements of ABP and CBFV taken over an estimation window of 5-60 beats are combined with the constraints imposed by the model, in order to generate estimates of ICP, *C*, and *R*. Our model shows that the latter two parameters are sensitive to the scale factor relating CBF and CBFV, while ICP – fortunately – is not. Our initial validation results obtain in work prior to the current project, on data collected from comatose patients suffering from major traumatic brain injury, and processed in batch mode, showed promising precision and accuracy.

Major new features of the current project are the following: we collect data from a different patient population than previously, namely those in neurointensive care with subarachnoid hemorrhage (for whom invasive ICP measurement as well as CBFV measurement are clinically indicated); we record under data collection protocols that we have helped to standardize, and under circumstances that we can record in detail; and we move towards real-time estimation.

IV. Status

We report here the status on each of the objectives listed in Section 2.

1. Develop a high-resolution data-acquisition infrastructure

In support of this objective, two key budgeted pieces of equipment were purchased during the first months of the project, namely the Component Neuromonitoring System (CNS, Moberg Research) and the Spencer Technologies ST^3 Transcranial Doppler (TCD) System. The roles of these two devices in our noninvasive ICP (nICP) estimation configuration are shown in Figure 1. The FDA-approved CNS device serves to collect data in a time-synchronized manner from the bedside Philips monitors as well as from the TCD.

We have tested the TCD system and verified the data streaming capability. Furthermore, we have tested the acquisition of CBFV data from both a unilateral probe, and a pair of bilateral probes affixed to a head frame. The data collected from the bilateral probes were remarkably stable with respect to even substantial head movement. While this is very encouraging for our purposes, the head frame might not always be usable in the neurocritical care setting, as it might interfere with other probes, scalp electrodes, and possible injury sites. This issue will be addressed as it arises.

In conjunction with the technical support staff at Spencer Technologies, we have determined that the signal delay of the CBFV waveform envelope is on the order of 10ms (8ms of data accumulation followed by FFT computation and other overhead).

We have obtained a loaner Philips bedside monitor from Philips Healthcare (Andover, MA) so that the device interfacing and signal characterization activities were able to proceed outside the constraints of the hospital environment.

We have been able to interface the Spencer TCD directly to the Philips bedside monitor and the CNS, and have continued our characterization of the signal delays along the signal path. Feeding the CBFV signals from the Spencer TCD to the Philips monitor and the CNS system introduces delays on the order of 200ms. Delays of this magnitude are not critical to our application of ICP estimation, as they preserve the association of the CBFV wavelet to the corresponding ABP wavelet.

In our laboratory setting, we have explored a variety of possible interface options for the Spencer TCD, including digital data streaming via a USB port and the analog output of the TCD machine for both offline and real-time processing of the (unilateral or bilateral) CBFV signal. The analog output is suited for feeding into the bedside monitor and for real-time processing. The digital data stream is suitable for feeding into the CNS, but currently not for real-time processing. Data stored on the Spencer TCD can also be used for offline processing.

We have extracted test data from the TCD, including the bilateral waveforms and annotations, converted to comma-separated format, which is suitable for further (offline) processing. We have also analyzed the waveform signal quality, filtered high-frequency noise, computed beat-onsets via our pre-processing algorithm, and computed mean, diastolic and systolic CBFV values.

We have received from Moberg Research a pre-release version of the software module interfacing the Spencer TCD with the CNS. Moberg is expecting to submit the software module shortly for FDA approval. The pre-release software module has the required functionality to receive the live data streams from the Spencer TCD and the Philips bedside monitor. In our testing, the two input devices provided a total of six parallel data channels: bilateral CBFV from the Spencer TCD, and ABP, ECG, Pleth, and SpO_2 from the Philips monitor. We have tested the data streaming to, and data archiving by, the CNS in a laboratory environment. We were able to stream data over extended periods of time, archive them, and later retrieve the data from the CNS.

Working with the biomedical engineering staff at our partner hospital, the Beth Israel Deaconess Medical Center (BIDMC), we have begun transitioning our tests of data streaming and integration from the laboratory into the neurocritical care environment. So far, our tests have focused on ensuring that our data streaming does not negatively impact the data flow on the clinical monitoring network.

We have also arranged and completed a TCD training session at BIDMC with an expert ultrasonographer to understand the proper operation of the Spencer TCD device and also understand how a transcranial ultrasound examination is performed. The session was attended by two MIT graduate students, as well as Dr. Kashif (an earlier postdoc on the project) and Dr. Heldt (the Principal Research Scientist currently playing a lead role in the project).

In the past month, we have worked closely with Dr. Eric Searls, the vascular neurologist at BIDMC who, along with his two neurology Fellows, will be overseeing the TCD recordings on the target patient population. Our objective was to familiarize them with the operation of the CNS system as an archiving agent for the TCD data. With this, and the developments described next, we are in a position to begin recording from patients in the coming two or three weeks. This recording will continue for the remainder of the project.

2. Establish a framework for archiving continuous monitoring data

Following time-consuming initial difficulties in developing avenues for deploying the instrumentation and archiving the resulting data, we have finally been able to establish an excellent framework for archiving the data needed for this project. As a first step, we obtained MIT IRB and DoD HRPO approval for use of the data in the Multiparameter Intelligent Monitoring in Critical Care II (MIMIC II) database (http://mimic.physionet.org). The database is described more fully in [2]. This is an

open-access, comprehensive clinical database to support work towards next-generation ICU patient-monitoring systems. The data comes from our partner hospital, the BIDMC, and is covered under a prior IRB with the PI of the MIMIC II project, Prof. Roger Mark at MIT. The database contains comprehensive clinical information from over 30,000 intensive care unit stays, including laboratory data, therapeutic intervention profiles such as vasoactive medication drip rates and ventilator settings, nursing progress notes, discharge summaries, radiology reports, provider order entry data, International Classification of Diseases (ICD-9) Codes, and, for a subset of about 5,000 patients, high-resolution vital-sign trends and waveform data from the patients' bedside monitors.

As the data that we are studying in this project is part of the routine clinical care of the target patient population at BIDMC, it is archived on MIMIC II in the normal fashion. The second key step for us was to establish the CNS system as the appropriate hardware interface for archiving the TCD data for transfer to the MIMIC II database. We have received clearance from the BIDMC biomedical engineering department for use of the CNS, and the use of the CNS for this purpose has subsequently been approved by an amendment to the MIMIC II IRB, separately from the current project. With the approved IRB to use the MIMIC II database in hand, we are in a position now to commence the data-acquisition from the hospital neurocritical care unit.

3. Seed the database and **4. Validate our noninvasive ICP estimates**
These two objectives remain to be met, as they cannot begin till data collection commences. We anticipate the start of data collection in the next two or three weeks, and will begin progress to these two objectives shortly thereafter.

5. Demonstrate real-time performance
We have made significant progress towards meeting this objective. Our ICP estimation routines have so far run in batch-mode on archived data. To make the algorithm operate in quasi real time at the bedside, we have re-designed and implemented its core modules. These changes allow computation on signal windows, and thus support a "buffer-mode" operation of the software for real-time estimation. In buffer-mode, a window of input data, usually around 60 beats, is accumulated. Once the buffer is filled with data, the estimation algorithm acts on the data buffer and produces one ICP estimate. The delay introduced in presenting the ICP estimate to the clinician is only on the order of 60 cardiac cycles and is therefore negligible in clinical applications.

We have also made progress towards developing a version of our ICP estimation algorithm to run in real-time on continuously streamed data. For this purpose, we have developed the signal pipeline that is schematically described in Figure 2. To acquire the ABP and CBFV data, we use a National Instruments DAQ-mx analog-to-digital (A/D) conversion card with a sampling rate of up to 10,000 samples/second, though operated nominally at 200 samples/second. This particular A/D card is USB enabled and can thus be connected to laptop or desktop computers. For our

prototyping purposes, we use the Matlab Data Acquisition Toolbox to control the data-acquisition step. Likewise, the signal-conditioning step and the ICP estimation algorithm are also implemented in the Matlab scientific computing environment.

We have tested the A/D front-end by streaming CBFV data from our ST^3 TCD system and ABP data from a Finapres noninvasive ABP monitoring system. We have also begun converting the estimation algorithm to run in real-time on data buffers of 60 beats. Non-overlapping 60 beats worth of ABP and CBFV data are stored in the front-end data buffer. Once the buffer is filled, the signal-conditioning algorithms are applied, and the ICP estimation algorithm is called to produce one estimate of mean ICP for each 60-beat data window. We are currently adapting the ICP estimation algorithm to be called each time the data buffer has been filled.

We developed a GUI-based tool for annotation correction, which can be incorporated into a real-time system for retrospective analysis of annotation quality, see Figure 3. We also developed a Matlab-based GUI for real-time ICP estimation system with options of changing filter parameters interactively and while the estimation routine is running, see Figure 4.

We are developing algorithms for automatic signal quality assessment. Currently, we have inserted a routine for checking spurious beat detections and missed beats, and are assigning signal quality labels to each ABP and CBFV wavelet. The estimation algorithm utilizes the beat labels to decide which beats are included/excluded in the estimation window.

We have developed a set of algorithms to automatically detect each ABP and CBFV wavelet and to determine if the input signals are of sufficient quality for ICP estimation. We are also currently evaluating time-domain based methods to achieve real-time beat-onset and artifact detection and flagging.

V. Key Research Accomplishments

Much of the work of the first year has involved setting up for data collection and archiving, and we anticipate our key research accomplishments to overlap with our forthcoming data collection and analysis. Nevertheless, the following items are worthy of note:

- Our earlier work on nICP estimation involved no hardware component at all, as we worked entirely with data collected and archived by a collaborator. Starting from nothing, we have built up a usable component-based data collection infrastructure that supports real-time nICP estimation.

- We have developed algorithms for various signal processing tasks, such as: detecting and flagging signal windows of low quality; time-aligning two pulsatile waveforms that were collected in a non-time-synchronized way.

- We have developed a frequency-domain approach to nICP estimation. Although further study and refinement are required, the initial results have been sufficiently encouraging to motivate additional work.

VI. Reportable Outcomes

The work supported by this grant has led to two invited presentations. In July 2012, we gave the Grand Rounds presentation at the U.S. Army Medical Research and Materiel Command/Telemedicine and Advanced Technology Research Center at Fort Detrick, MD. The presentation was entitled "Model-based noninvasive intracranial pressure estimation." In September 2012, we presented on the topic of "Time- and frequency-domain approaches to model-based noninvasive intracranial pressure estimation" at the workshop on "Information derived from the arterial blood pressure waveform and its clinical significance" at the 34th Annual International Conference of the IEEE Engineering in Medicine and Biology Conference.

The grant also supported the career development of Ms. Irena Hwang and Dr. Faisal Kashif. Ms. Hwang's Master's thesis was on the topic of "Frequency domain model-based intracranial pressure estimation." After graduating from MIT in June 2012, she joined the PhD program of the Department of Electrical Engineering at Stanford University. In his doctoral thesis, Dr. Kashif laid the groundwork for the current project. Dr. Kashif was as a Postdoctoral Associate on this project from September 2011 till the end of April 2012, when he joined Masimo Corporation at their corporate headquarters in Irvine, CA, as a Senior Research Engineer.

The work preformed under this grant also fed into a recent grant application to the National Institutes of Health, entitled "Noninvasive intracranial pressure determination in pediatric patients," which seeks to translate the work conducted under the current grant to infants, children, and young adolescents. Traumatic brain injury is the leading cause of death and disability in children born healthy. A noninvasive approach to ICP determination would significantly improve neurological, neurocritical, and neurosurgical care for these patients.

VII. Conclusion

We anticipate finally beginning collection of patient data in the next two or three weeks, having overcome various obstacles related to setting up data collection in our partner hospital, and to establishing the route to an appropriate database. The feed to MIMIC II gives us access to an extensible and widely accessible database, which will be of great value to other ICP researchers as well.

Our ultimate aim, beyond the scope of the present project (although we are making valuable steps towards it), is to enable a fully noninvasive nICP estimation modality, using a finger cuff measurement of ABP, as in Figure 5.

VIII. References

1. Kashif, F.M., et al., *Model-based noninvasive estimation of intracranial pressure from cerebral blood flow velocity and arterial pressure.* Sci Transl Med, 2012. **4**(129): p. 129ra44.
2. Saeed, M., et al., *Multiparameter Intelligent Monitoring in Intensive Care II: a public-access intensive care unit database.* Crit Care Med, 2011. **39**(5): p. 952-60.

IX. Figures

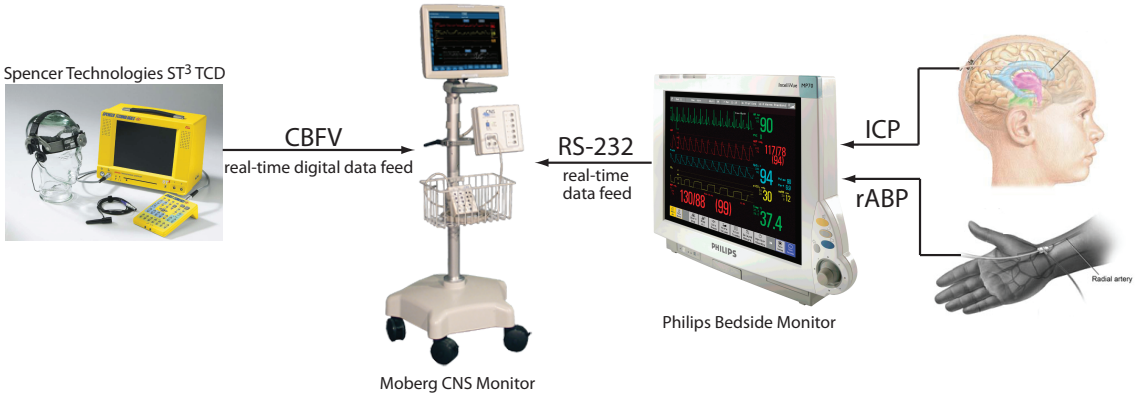

Figure 1: Data collection infrastructure in the neurocritical care unit to support the data collection under this research project.

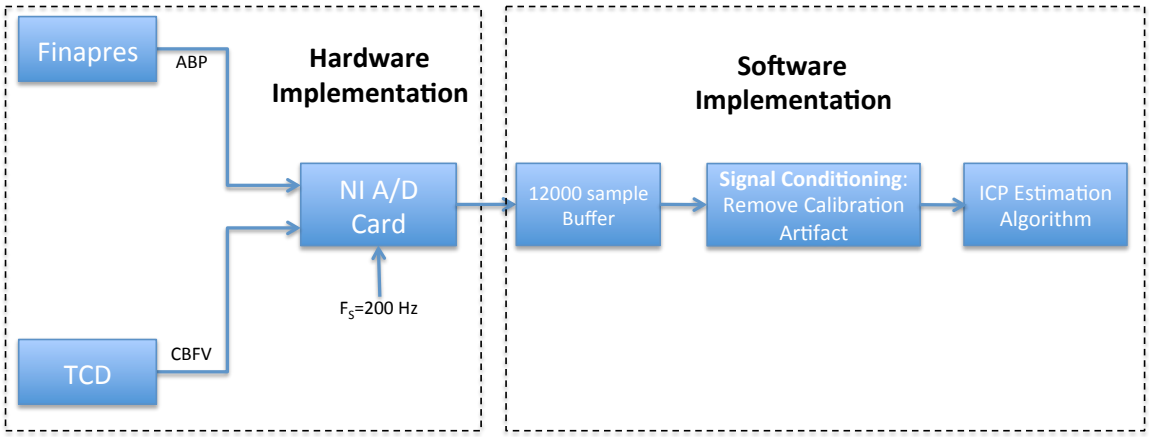

Figure 2: Signal-processing steps for real-time ICP estimation.

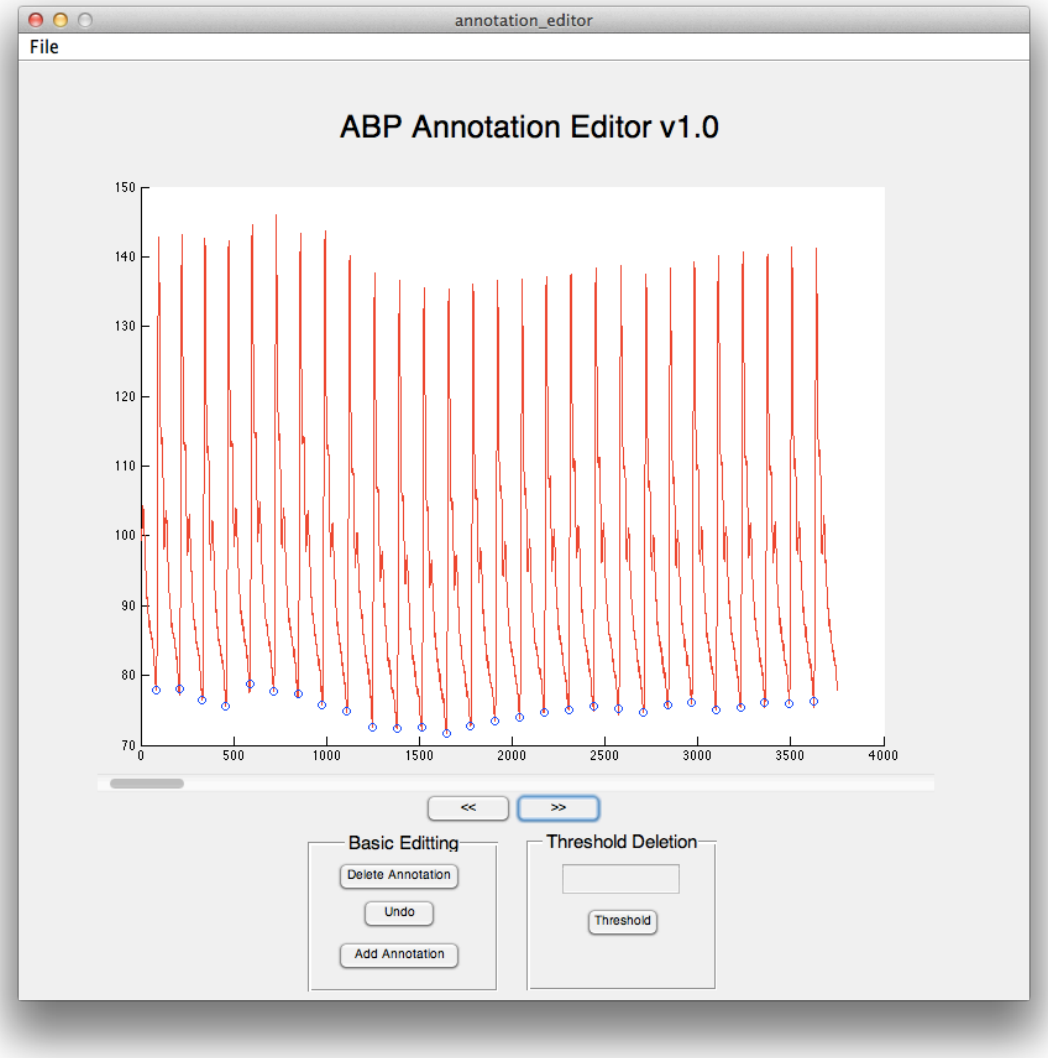

Figure 3: Graphical User Interface for retrospective analysis of waveform annotation process. Shown are the beat-onset annotations for the arterial blood pressure (ABP) waveform.

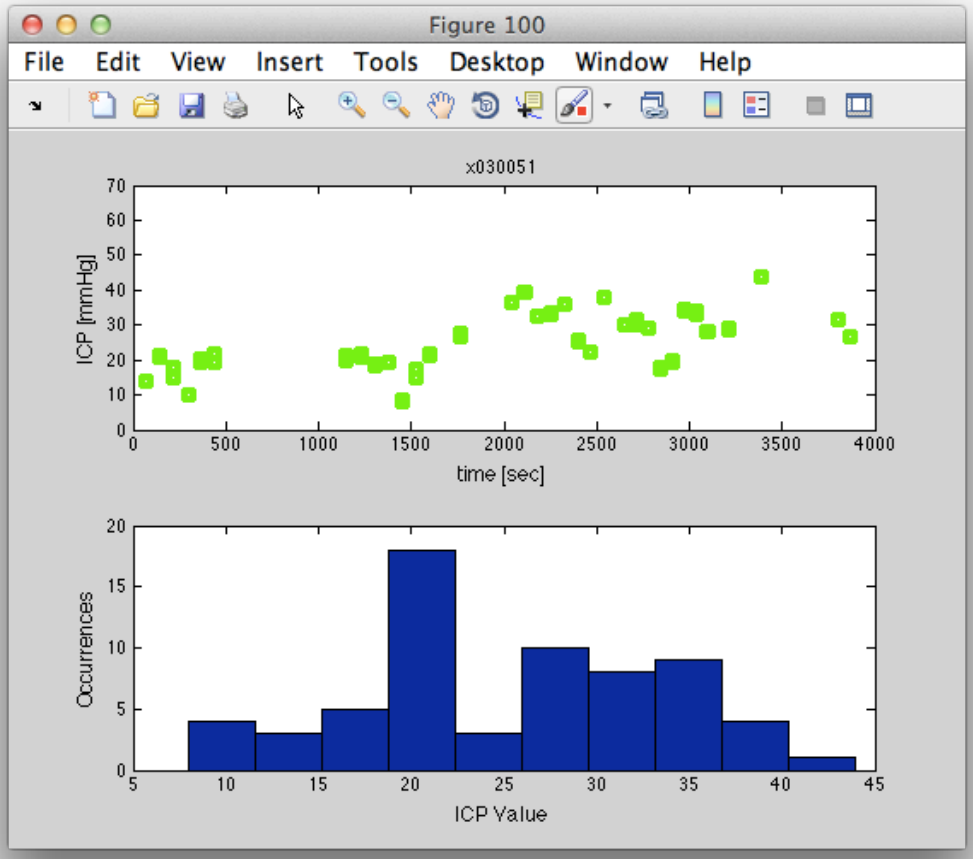

Figure 4: Noninvasive ICP estimation results. Top panel: estimates as a function of time; bottom panel: histogram of noninvasive ICP estimates.

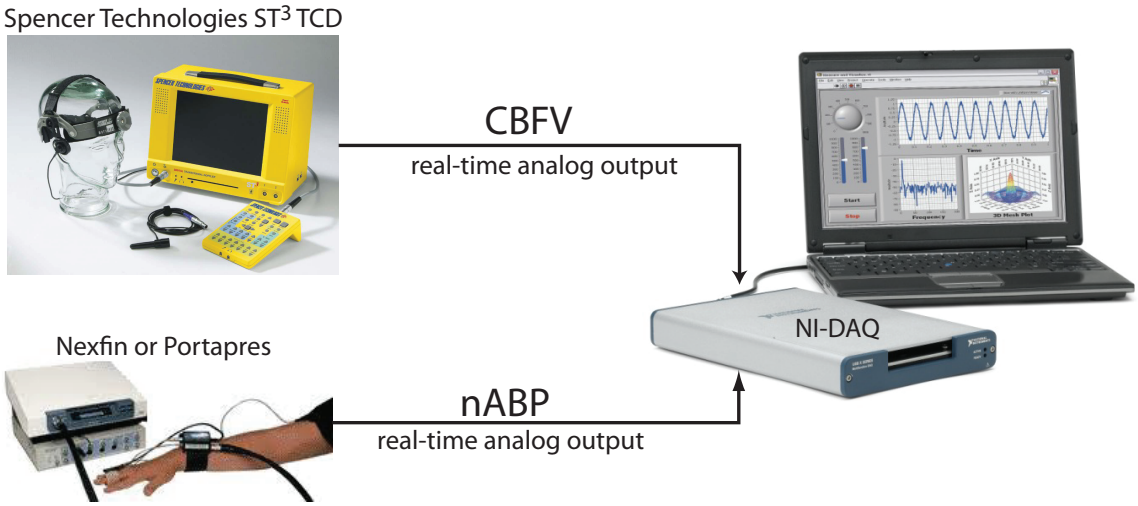

Figure 5: Data collection set-up for real-time ICP estimation from cerebral blood flow velocity and noninvasive arterial blood pressure waveform measurements.